Amendment to the Specification:

Please replace paragraphs [0002], [00003], [0046], [0075], [0103], [0104], [0110], [0111], [0112], [0113], [0122], [0123], [0125], [0126], [0129], [0135], [0159], [0160], [0162], [0164], [0169], and [0171] and the Abstract with the following amended paragraphs:

[0002] The present invention relates to methods for treating atypical tissues, such as ~~hyperplasic~~ hyperplastic tissues, cysts and neoplasms (including tumors and cancers) and for preventing the development of, or for causing the regression or remission of, atypical tissues, cysts and neoplasms. In particular, the present invention relates to methods for treating mammary gland disorders, such as mammary gland cysts and neoplasms, both benign and cancerous, as well as for treating ~~hyperplasic~~ hyperplastic and/or hypertonic mammary gland cells by local administration of a Clostridial toxin to or to the vicinity of the afflicted mammary gland tissue.

[0003] It is known that many ~~hyperplasic~~ hyperplastic tissues can, if not treated, develop into cancerous tissues, for example (1) different hyperplasia, ~~metaplasic~~ metaplastic or atypical breast tissues can develop into cancers (see e.g. Ellis I. O., et al, Tumors of the Breast, chapter 16 (pages 865-930) of "Diagnostic Histopathology of Tumors", volume 1, edited by Fletcher C. D. M., second edition, Churchill Livingstone (2000), discussed further infra, as well as Fabian C. J. et al Beyond tamoxifen new endpoints for breast cancer chemoprevention, new drugs for breast cancer prevention, Ann NY Acad Sci 2001 Dec;952:44-59); (2) ~~hyperplasic~~ hyperplastic intestinal tissues, such as polyps can transform into carcinomas (see e.g. Der, R. et al Gastric Neoplasms, chapter 5 (pages 105-144) of Chandraspma, P., "Gastrointestinal Pathology", Appleton & Lange (1999), in particular pages 106-107; (3) oral and oropharyngeal epithelial hyperplasia indicates a precancerous lesion. Sunaga H., et al. Expression of granulocyte colony-stimulating factor receptor and platelet-derived endothelial cell growth factor in oral and oropharyngeal precancerous lesions.

Anticancer Res 2001 July-August; 21 (4B):2901-6; (4) Endometrial ~~hyperplasic~~ hyperplastic tissue is a precancerous tissue. Sivridis E. et al., Prognostic aspects on endometrial hyperplasia and neoplasia, Virchows Arch 2001 August; 439(2):118-26, and; (5) kidney and prostate cell hyperplasia has been documented as a factor leading to development of cancerous cells. Van Poppel, H., et al., Precancerous lesions in the kidney Scand J Urol Nephrol Suppl 2000; (205):136-65.

[0046] It is known to use a botulinum toxin to treat: intrathecal pain (see e.g. U.S. Pat. No. 6,113,915); paragangliomas (see e.g. U.S. Pat. No. 6,139,845); otic disorders (see e.g. U.S. Pat. No. 6,265,379); pancreatic disorders (see e.g. U.S. Pat. Nos. 6,143,306 and 6,261,572); migraine (see e.g. U.S. Pat. No. 5,714,468); smooth muscle disorders (see e.g. U.S. Pat. No. 5,437,291); prostate disorders, including prostatic hyperplasia (see e.g. WO 99/03483 and Doggweiler R., et al Botulinum toxin type A causes diffuse and highly selective atrophy of rat prostate, Neurourol Urodyn 1998;17(4):363); autonomic nerve disorders, including ~~hyperplasic~~ hyperplastic sweat glands (see e.g. U.S. Pat. No. 5,766,606); wound healing (see e.g. WO 00/24419); reduced hair loss (see e.g. WO 00/62746); skin lesions (see e.g. U.S. Pat. No. 5,670,484), and; neurogenic inflammatory disorders (see e.g. U.S. Pat. No. 6,063,768). U.S. Pat. No. 6,063,768 cursorily discloses at column 6 lines 39-42 treatment of the inflammatory joint condition pigmented villonodular synovitis and a particular type of joint cancer, synovial cell sarcoma. Column 6, line 53 of U.S. Pat. No. 6,063,768 also discloses, without further explanation, that "tumors" can be treated.

[0075] Diverse ~~hyperplasic~~ hyperplastic and neoplastic mammary gland cells are influenced by cholinergic mechanisms. Thus, it has been discovered that there is a "cholinergic mechanism in the alveolar cells activity". Balakina G. B., et al., Localization of choline acetyltransferase in the alveolar portion of the mammary gland of the white mouse, Arkh Anat Gistol Embriol 1986 April; 90(4):73-7. Additionally, there is cholinergic influence upon both mammary dysplasia (fibrocysts) and mammary carcinoma tissues (Dorosevich A. E., et al., Autonomic nerve endings and their cell microenvironment as

one of the integral parts of the stromal component in breast dysplasia and cancer, Arkh Patol 1994 November-December; 56(6):49-53), as well as "a direct cholinergic stimulation of smooth muscle cells" in mammary arteries (Pesic S., et al., Acetylcholine-induced contractions in the porcine internal mammary artery; possible role of muscarinic receptors, Zentralbl Veterinarmed A 1999 October; 46(8): 509-15).

[0103] What is needed therefore is an effective, non-surgical ablation, non-radiotherapy therapeutic method for treating mammary gland neoplasms and precancerous ~~hyperplasic~~ hyperplastic mammary gland tissues.

[0104] The present invention meets this need and provides an effective, non-surgical ablation, non-radiotherapy therapeutic method for treating various precancerous as well as cancerous mammary gland tissues. Thus, the present invention encompasses methods for treating atypical tissues, such as ~~hyperplasic~~ hyperplastic tissues, cysts and neoplasms (including tumors and cancers) and for preventing the development of, or for causing the regression or remission of, atypical tissues, cysts and neoplasms. In particular, the present invention encompasses methods for treating mammary gland disorders, such as mammary gland cysts and neoplasms, both benign and cancerous, as well as for treating ~~hyperplasic~~ hyperplastic and/or hypertonic mammary gland cells by local administration of a Clostridial toxin to or to the vicinity of the afflicted the mammary gland tissue.

[0110] Additionally, the present invention encompasses a method for preventing development of a mammary gland neoplasm, the method comprising the step of local administration of a botulinum toxin to a ~~hyperplasic~~ hyperplastic or hypertonic mammary gland tissue, thereby reducing a secretion from the ~~hyperplasic~~ hyperplastic or hypertonic mammary gland tissue and preventing the ~~hyperplasic~~ hyperplastic or hypertonic mammary gland tissue from developing into a neoplasm. In this method the botulinum toxin is administered in an amount of between about 10^{-3} U/kg and about 2,000 U/kg and the botulinum toxin is selected from the group consisting of botulinum

toxin types A, B, C, D, E, F and G. The botulinum toxin can be locally administered by direct injection of the botulinum toxin into the ~~hyperplasic~~ hyperplastic or hypertonic mammary gland tissue.

[0111] To reiterate, a method for preventing development of a mammary gland neoplasm can comprise the step of local administration of a therapeutic amount of a botulinum toxin type A to the precancerous ~~hyperplasic~~ hyperplastic or hypertonic mammary gland tissue of a human patient, thereby preventing development of a mammary gland neoplasm.

[0112] Alternately, a method for preventing development of a neoplasm can comprise the step of local administration of between about 10^{-3} U/kg and about 2000 U/kg of a botulinum toxin to a ~~hyperplasic~~ hyperplastic tissue, wherein the botulinum toxin reduces a secretion from the ~~hyperplasic~~ hyperplastic tissue by inhibiting a vesicle mediated exocytosis from the precancerous ~~hyperplasic~~ hyperplastic tissue, thereby preventing development of the ~~hyperplasic~~ hyperplastic tissue into a neoplasm. The ~~hyperplasic~~ hyperplastic tissue can comprise a substrate for the botulinum toxin selected from the group of vesicle membrane docking proteins consisting of a 25 kiloDalton synaptosomal associated protein (SNAP-25), synaptobrevin and syntaxin. Furthermore, the botulinum toxin can be administered in an amount of between about 1 U and about 40,000 U, such as between about 10^{-3} U/kg and about 35 U/kg, between about 10^{-2} U/kg and about 25 U/kg, between about 10^{-2} U/kg and about 15 U/kg or between about 1 U/kg and about 10 U/kg. and the local administration of the botulinum toxin is carried out by implantation of a botulinum toxin implant into or onto the body of the breast tissue.

[0113] A detailed embodiment of the present invention is a method for preventing development of a mammary gland carcinoma (that is by preventing the development of a benign [though ~~hyperplasic~~ hyperplastic, ~~metaplasic~~ metaplastic or atypical] precancerous breast tissue into a malignant neoplasm or carcinoma), the method

comprising the step of local administration of between about 10^{-3} U/kg and about 2000 U/kg of a botulinum toxin type A to a hyperplastic, ~~metaplasic~~ metaplastic or atypical breast tissue (such as an apocrine cell lined cyst) of a human patient, wherein the breast tissue comprises a substrate for the botulinum toxin selected from the group of vesicle membrane docking proteins consisting of a 25 kiloDalton synaptosomal associated protein (SNAP-25), synaptobrevin and syntaxin, and wherein the botulinum toxin acts upon the substrate to reduce a secretion from the afflicted breast tissue.

[0122] The present invention is based upon the discovery that ~~hyperplasic~~ hyperplastic, hypertonic, cystic and/or neoplastic tissues can be treated with a Clostridial toxin to thereby reduce or eliminate the hyperplasia, hypertonia, cystic and/or neoplastic condition. The tissue treated can be benign or malignant and hyperplasia includes a hypertonic condition. The present invention is therefore applicable to the treatment of conditions which include breast cancer, cystic breast disease, lung cancer, adencarcinomas, ovarian cancer, oral and oropharyngeal cancers, pancreatic cysts and pancreatic cancer, prostate cancer, kidney cancer, GI tract cancer, testicular cancer and cysts, lymph node cancer, endometrial cancers, as well as to ~~hyperplasic~~ hyperplastic, ~~metaplasic~~ metaplastic, atypia and dysplasic precancerous tissues of such organs and glands.

[0123] Additionally, excessively secreting cells (~~hyperplasic~~ hyperplastic or hypertonic) wherein the secretory activity is controlled or influenced by one or more of the botulinum toxin substrates can be treated by a method within the scope of the present invention so as to prevent the development of the ~~hyperplasic~~ hyperplastic or hypertonic secretory tissue into a neoplasm. In the target tissue the proteolytic light chain of the botulinum toxin is internalized.

[0125] Thus a preferred embodiment of the present invention is a method for treating a precancerous mammary gland disorder, such as breast cysts, sclerosing adenosis, papillomas, fibroadenomas (hyperplasia lobules) and blunt duct adenosis. By

precancerous it is meant that the afflicted breast tissue is not-malignant (i.e. is not cancerous), although it can be ~~hyperplasic~~ hyperplastic, hypertrophic or ~~metaplasic~~ metaplastic, and that the presence of the precancerous tissue increases the risk to the patient of development of a breast cancer.

[0126] Thus, cholinergically innervated target tissues can be treated by local administration of a Clostridial toxin, such as a botulinum toxin. By local administration it is meant that the neurotoxin is administered directly into, or to the vicinity of the target tissue (i.e. a precancerous breast tissue) or local tissue area to be treated. Local administration includes injection of the neurotoxin directly into the afflicted tissue. Non-cancerous (benign), precancerous, cancerous (malignant) ~~hyperplasic~~ hyperplastic and/or hypertonic secretory tissues can be treated by a method within the scope of the present invention. Nodular or diffuse hyperplasia which precedes tumor development can be treated by the present method.

[0129] The specific dosage appropriate for administration is readily determined by one of ordinary skill in the art according to the factors discussed above. The dosage can also depend upon the size of the tumor to be treated or denervated, and the commercial preparation of the toxin. Additionally, the estimates for appropriate dosages in humans can be extrapolated from determinations of the amounts of botulinum required for effective denervation of other non-neoplastic tissues. Thus, the amount of botulinum A to be injected is proportional to the mass and level of activity of the breast tissue to be treated. Generally, between about 0.01 and 2000 units per kg of patient weight of a botulinum toxin, such as botulinum toxin type A, can be administered to effectively accomplish a toxin induced target tissue atrophy upon administration of the neurotoxin at or to the vicinity of the breast target tissue. Less than about 0.01 U/kg of a botulinum toxin does not have a significant therapeutic effect while more than about 2000 U/kg or 35 U/kg of a botulinum toxin B or A, respectively, approaches a toxic dose of the specified botulinum toxin. Careful placement of the injection needle and a low volume of neurotoxin used prevents significant amounts of botulinum toxin from appearing

systemically. A more preferred dose range is from about 0.01 U/kg to about 25 U/kg of a botulinum toxin, such as that formulated as BOTOX®. The actual amount of U/kg of a botulinum toxin to be administered depends upon factors such as the extent (mass) and level of activity of the i.e. ~~hyperplasic~~ hyperplastic breast tissue to be treated and the administration route chosen. Botulinum toxin type A is a preferred botulinum toxin serotype for use in the methods of the present invention.

[0135] Hence, by practice of the present disclosed invention, non-cholinergic nerve fibers as well as non or poorly innervated secretory neoplasms can be treated by use of an appropriately higher concentration of a botulinum toxin to bring about therapeutic atrophy of secretory neoplasms (i.e. treatment of functional (catecholamine secreting) paragangliomas) and ~~hyperplasic~~ hyperplastic chromaffin cells.

[0159] Treatment of Hypertonic or ~~Hyperplasic~~ Hyperplastic Tissues with a Botulinum Toxin.

[0160] Local administration of a botulinum toxin directly to or to the vicinity of a hypertonic or ~~hyperplasic~~ hyperplastic target tissue can be accomplished by several methods. As set forth above a dermal or subdermal target tissue, such as breast tissue, can be treated by direct injection or by placement of a toxin implant. Visceral sites, such as a visceral neuroblastoma, can also be easily accessed. For example, endoscopy for diagnostic and therapeutic purposes is well known.

[0162] If the pancreatic duct is not accessible or does not decompress, a percutaneous needle, imaging guided (i.e. by ultrasound or computed tomography) can also be used for transabdominal injection of a neurotoxin directly into pancreatic tissue. Thus, percutaneous needle aspiration for pancreatic biopsy is a known technique and aspiration can be reversed to accomplish the desired toxin injection. Thus, an insulinoma or hypertonic or ~~hyperplasic~~ hyperplastic pancreatic tissue can be treated by local administration of from 1[[ ]]500 units of a botulinum toxin to the pancreatic target

tissue. Neoplastic or hyperplastic lung, intestinal and ovarian target tissue can likewise be treated[[,]].

[0164] Stereotactic procedures can be used for precise intracranial administration of neurotoxin in aqueous form or as an implant to treat a ~~hyperplasic~~ hyperplastic or hypothalamus or pituitary target tissue. A cranial neuroblastoma is also treated in this manner. Thus, intracranial administration of a botulinum toxin can be carried out as follows.

[0169] Computer-aided atlas-based functional neurosurgery methodology can be used to accurately and precisely inject the desired neurotoxin or implant a neurotoxin controlled release implant. Such methodologies permit three-dimensional display and real-time manipulation of hypothalamic structures. Neurosurgical planning with mutually preregistered multiple brain atlases in all three orthogonal orientations is therefore possible and permits increased accuracy of target definition for neurotoxin injection or implantation, reduced time of the surgical procedure by decreasing the number of tracts, and facilitates planning of more sophisticated trajectories. See e.g. Nowinski W. L. et al., Computer-Aided Stereotactic Functional Neurosurgery Enhanced by the Use of the Multiple Brain Atlas Database, IEEE Trans Med Imaging 19(1);62-69:2000. Thus, an pituitary tumor or hypertonic or ~~hyperplasic~~ hyperplastic pituitary tissue can be treated by local administration of from 1 to 500 units of a botulinum toxin to the pituitary target tissue.

[0171] (1) the invention renders unnecessary surgery for effective treatment of diverse breast disease, including ~~hyperplasic~~ hyperplastic, hypertonic and ~~metaplasic~~ metaplastic breast tissues.